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Crystal Structures of Mismatch Repair Protein MutS and its Complex with a Substrate DNA

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ABSTRACT: DNA mismatch repair is critical for increasing replication fidelity in organisms ranging from bacteria to humans. MutS protein, a member of the ABC ATPase superfamily, recognizes mispaired and unpaired bases in duplex DNA and initiates mismatch repair. Mutations in human MutS genes cause a predisposition to hereditary nonpolyposis colorectal cancer as well as sporadic tumors. Here we report the crystal structures of a MutS protein and a complex of MutS with a heteroduplex DNA containing an unpaired base. The structures reveal the general architecture of members of the MutS family, an induced-fit mechanism of recognition between four domains of a MutS dimer and a heteroduplex kinked at the mismatch, a composite ATPase active site composed of residues from both MutS subunits, and a transmitter region connecting the mismatch-binding and ATPase domains. The crystal structures also provide a molecular framework for understanding hereditary nonpolyposis colorectal cancer mutations and for postulating testable roles of MutS.